

NOVEL ANTI-ARRHYTHMIC AND HEART FAILURE DRUGS THAT TARGET THE
LEAK IN THE RYANODINE RECEPTOR (RYR2)

ABSTRACT OF THE DISCLOSURE

[00143] The present invention provides novel 1,4-benzothiazepine intermediates and
5 derivatives, methods for synthesizing same, and methods for assaying for same. The present
invention also provides methods for using these novel compounds to limit or prevent a
decrease in the level of RyR2-bound FKBP12.6 in a subject; to prevent exercise-induced
sudden cardiac death in a subject; and to treat or prevent heart failure, atrial fibrillation, or
exercise-induced cardiac arrhythmia in a subject. The present invention further provides
10 methods for identifying an agent that enhances binding of RyR2 and FKBP12.6, and agents
identified by these methods. Additionally, the present invention provides methods for
identifying agents for use in treating or preventing heart failure, atrial fibrillation, or exercise-
induced cardiac arrhythmia, and in preventing exercise-induced sudden cardiac death. Also
provided are agents identified by such methods.